SOME MECHANISMS OF BRAIN EDEMA STUDIED IN A KAINIC ACID MODEL

F. SEITELBERGER, H. LASSMANN and O. HORNykiewicz

Neurological Institute and 
Institute for Biochemical Pharmacology,
University Vienna, 17 Schwarzhansienstrasse,
A-1090 Vienna, Austria

Key words: kainic acid, brain edema, epilepsy

Abstract. Kainic acid (KA) is a potent neuroexcitatory drug widely used in the experimental study of seizure activity. Subcutaneous injection of KA into rats (10 mg/kg in saline 10 mg/ml; pH 7.0) induced longlasting status epilepticus followed by damage of CNS tissue in the entorhinal/pyriform cortex and in the hippocampus. The studies covered by this report demonstrated the formation of cytotoxic brain edema characterized by massive swelling of perineuronal and perivascular astroglia with microcirculation disturbance after KA injection, resulting in parenchymal necrosis of the affected region; furthermore perivenous hemorrhages and necroses corresponding to herniation lesions of the brain appear. Tracer studies with Na-fluorescein, Evans blue, albumin, and horseradish peroxidase revealed only a mild increase in the permeability of cerebral vessels, topographically unrelated to areas of brain edema. Treatment of brain edema with dexamethasone did not influence the incidence and severity of edematous brain damage. Treatment with mannitol, however, completely prevented the lesion in 54% of animals injected with KA. The present results indicate that brain edema plays an important role in the pathogenesis of epileptic brain damage following systemic KA intoxication. It is suggested that in this model brain edema develops due to massive ionic imbalance caused by KA induced persistent neuronal excitation. In addition the model demonstrates the possible patho-
genetic role of selective astrocytic swelling in the production of local hippocampal ischemia followed by herniation and its sequels. Such pathology originating from astrocytes probably may occur also in closed brain injury.

INTRODUCTION

Kainic acid (KA), a rigid analogue of glutamic acid, is a cytotoxic agent, causing strong excitation of neurons of the mammalian central nervous system (2, 6). Systemic administration of KA leads to a clinical picture of secondarily generalized limbic seizures, accompanied by nerve cell loss and reactive gliosis mainly in the hippocampus (the CA1 and CA3 sector) and in the entorhinal and pyriform cortex (1, 5, 7). Although it is generally believed that KA-induced brain damage is due to mechanisms directly related to the action of the drug (1, 5), we recently found evidence that brain edema with subsequent disturbance of brain microcirculation may play an essential role in its pathogenesis (3, 7).

MATERIAL AND METHODS

Experimental epilepsy was induced in rats by subcutaneous injection of KA (10 mg/kg in saline 10 mg/ml: pH 7.0). The clinical severity of seizure activity was scored (3, 7) and the animals were sampled for neuropathological and neurochemical studies at various time intervals between 1 h and 20 days after injection of the drug. Morphological studies included light and electron microscopy and blood brain barrier studies with sodium fluoresceine, Evans blue, horseradish peroxidase and endogenous albumin (3). In addition neurotransmitters (noradrenaline, dopamine, serotonin), transmitter metabolites (homovanillic acid, 5-hydroxyindol-acetic acid) and neuronal transmitter enzymes (glutamate decarboxylase, choline acetyltransferase) were determined neurochemically (7). Treatment of KA-induced brain edema was performed with dexamethasone or mannitol at various doses and schedules (3, 7).

RESULTS

Systemic injection of KA resulted in longlasting, secondary generalized limbic seizures. First seizures appeared 1-1.5 h and reached maximal intensity 2 and 3 h after subcutaneous injection of the drug. During the following hours epileptic seizures diminished gradually and after 1 day only rare seizures were noted either spontaneously or induced by noise or handling animals (7).
Neurochemically, during the stage of generalized status epilepticus massive turnover of neurotransmitters was noted, expressed by a decrease of noradrenaline and dopamine and increase of transmitter metabolites like 5-hydroxyindol-acetic acid and homovanillic acid (7). Neuropathologically, at this stage some dark condensed neurons were found together with massive swelling of astrocytes in the limbic system, resulting in compression of local blood vessels in edematous areas (3). Three days after KA-injection and later, neurotransmitter levels and transmitter metabolites returned to normal values indicating normalization of transmitter turnover (7). However, neuronal transmitter enzymes, like glutamate decarboxylase, were permanently decreased in the limbic system which suggests degeneration of nerve cells in this region.

In neuropathology nerve cell loss and incomplete parenchymal necrosis was present especially in the hippocampus, the amygdala and the entorhinal/pyriform cortex. In addition multiple perivenous hemorrhages were found in the necrotic areas, suggesting herniation damage due to brain edema during status epilepticus (3, 4, 7). Treatment of brain edema with dexamethasone did not change the clinical appearance of KA-induced seizures and had no effect on the incidence and severity of KA-induced permanent brain lesions. However, mannitol treatment showed a clear-cut therapeutic effect (Table I). As a matter of fact irreversible brain lesions due to KA as determined neuropathologically as well as neurochemically were completely prevented in more than 50% of the animals treated with mannitol (3).

<table>
<thead>
<tr>
<th>Induction of seizures</th>
<th>Treatment of seizures</th>
<th>Schedule of treatment</th>
<th>Number of animals</th>
<th>Nerve cell loss</th>
<th>Necrosis</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA</td>
<td>mannitol</td>
<td>1.5 and 7 h</td>
<td>30</td>
<td>46% (14/30)</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>2×1.5 g/kg</td>
<td>after KA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KA</td>
<td>saline</td>
<td>1.5 and 7.5 h</td>
<td>33</td>
<td>93% (31/31)</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>2×6 ml/kg</td>
<td>after KA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ø</td>
<td>mannitol</td>
<td>2× in 6 h interval</td>
<td>6</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>KA</td>
<td>dexamethasone 3 daily doses</td>
<td></td>
<td>10</td>
<td>100% (10/10)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>2 mg/kg/d</td>
<td>of 0.6 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ø</td>
<td>dexamethasone 3 daily doses</td>
<td></td>
<td>6</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg/d</td>
<td>of 0.6 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

The pathogenesis of the lesion picture in our experiments could be reconstructed as follows: extreme excitotoxic overactivity of neurons in the epileptic state induced by systemic KA-injection leads to liberation of excessive potassium, lactic acid and other metabolites corresponding to the pathogenesis of neuronal necroses in ischemic brain damage. These products also cause the massive swelling of astroglial cells with subsequent disturbance of microcirculation which then results in tissue necrosis and hemorrhage formation. Furthermore the general brain swelling causes dislocation of parts of the brain, impression of prominent parts of the skull into the brain and decrease of brain circulation especially in drainage veins. This produces secondary lesions in form of hemorrhages and circulatory brain tissue necroses. Therefore the final epileptic brain damage following systemic KA-injection is caused mainly by factors other than by direct KA-induced neurotoxicity. KA-produced overactivity of neurons only starts the cascade of secondary tissue alterations as edema, microcirculatory disturbance and subsequent hypoxia which similar to circulatory ischemic events cooperate in the pathogenesis of irreversible epileptic brain damage.

This concept seems corroborated by the results of our therapeutic trials. The administration of dexamethasone had no effect at all or even worsened and increased the bleeding. Application of mannitol, a substance which reverts the osmotic gradient between CNS and serum, in about 50% of the animals, however, resulted in total prevention of the described morphological changes. The relatively low proportion of successfully treated animals may be explained by an all or nothing-phenomenon in mannitol-treatment, i.e. by the fact that the pathogenic effect of KA is temporarily limited, yet initiates via the cytotoxic brain edema the progressive secondary anoxic-ischemic tissue changes. This process only for a restricted time can be reserved by the effect of mannitol on the intracellular edema. After a certain time, however, the pathogenic avalanche no longer can be stopped and mannitol becomes ineffective.

Finally it should be mentioned that these findings seem to be able to finish the old dispute between the theories of Spielmeyer and of the Vogt's respectively about the pathogenesis of regional lesions in the hippocampus by epileptic seizures. Spielmeyer argued that a local circulatory disorder in the so-called Sommer's sector of Ammon's horn, which corresponds to sector CA1, was the cause, whereas the Vogt's postulated that the vulnerability of CA1 was related to the intrinsic metabolic properties of the griseum. Both theories appear to be correct in certain respects. Metabolic characters of the CA1 neurons — including recep-
tor-transmitter relation — obviously are responsible for their proneness to synchronized hyperfunction that subsequently induces cytotoxic brain edema. This edema, however, represents the crucial pathogenetic factor as being connected with a disturbance of microcirculation which finally produces brain tissue damage in the respective areas. Thus a metabolic factor as well as a circulatory disorder are responsible for the eventual morphological lesion.

REFERENCES


